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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/774,047	02/06/2004	Zhenwei Miao	4056.1066 US1	4991
38473 7590 03/20/2008 ELMORE PATENT LAW GROUP, PC 515 Groton Road Westford, MA 01886				
EXAMINER JARRELL, NOBLE E				
ART UNIT		PAPER NUMBER		
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03/20/2008		PAPER		

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary

Application No.

10/774,047

Applicant(s)

MIAO ET AL.

Examiner

Noble Jarrell

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Period for Reply -- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

- 1) ☒ Responsive to communication(s) filed on 01 February 2008.
- 2a) ☐ This action is **FINAL**. 2b) ☒ This action is non-final.
- 3) ☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

- 4) ☒ Claim(s) 1-70, 74-87 is/are pending in the application.
- 4a) Of the above claim(s) 34, 48 and 60 is/are withdrawn from consideration.
- 5) ☐ Claim(s) _____ is/are allowed.
- 6) ☒ Claim(s) 1-33, 35-47, 49-59, 61-70 and 74-87 is/are rejected.
- 7) ☐ Claim(s) _____ is/are objected to.
- 8) ☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

- 9) ☐ The specification is objected to by the Examiner.
- 10) ☐ The drawing(s) filed on _____ is/are: a) ☐ accepted or b) ☐ objected to by the Examiner.
- Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).
- Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).
- 11) ☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

- 12) ☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).
- a) ☐ All b) ☐ Some * c) ☐ None of:
1. ☐ Certified copies of the priority documents have been received.
 2. ☐ Certified copies of the priority documents have been received in Application No. _____.
 3. ☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

- 1) ☒ Notice of References Cited (PTO-892)
- 2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
- 3) ☐ Information Disclosure Statement(s) (PTO/SB08)
- Paper No(s)/Mail Date _____
- 4) ☐ Interview Summary (PTO-413)
- Paper No(s)/Mail Date _____
- 5) ☐ Notice of Informal Patent Application
- 6) ☐ Other: _____

DETAILED ACTION

Election/Restrictions

1. Applicant's election with traverse of group I in the reply filed on 2/1/2008 is acknowledged. The traversal is on the ground(s) that there is a common core for all compounds of formula I. This is not found persuasive because analysis of formula I when variable L is absent, there are 45 possible ring elemental sequences in STN that can occur (3 rings for azetidine, pyrrolidine, and piperidine; 3 for when variable s is 0, 1, or 2; and 5 for the big ring, depending on what integer variable j is). If one factors in the other possible groups for variable L, then the number of common grows. Each ring elemental sequence represents a different core. Thus, there is no common core to all of the possible groups for variable L. Applicants also argue that unity exists in the instant case. However, it is noted that unity only applies to national stage cases, not U.S. 111 cases. In addition, as a result of the election, groups 34, 48, and 60 are considered withdrawn.

The requirement between the compounds is still deemed proper.

2. Claims 1-33, 35-47, 49-59, 61-65, and 76-87 are directed to an allowable product. Pursuant to the procedures set forth in MPEP § 821.04(B), claims 66-70 and 74-75, directed to the process of making or using an allowable product, previously withdrawn from consideration as a result of a restriction requirement, are hereby rejoined and fully examined for patentability under 37 CFR 1.104.

Because all claims previously withdrawn from consideration under 37 CFR 1.142 have been rejoined, **the restriction requirement as set forth in the Office action mailed on 1/8/08 is hereby withdrawn.** In view of the withdrawal of the restriction requirement as to the rejoined inventions, applicant(s) are advised that if any claim presented in a continuation or divisional application is anticipated by, or includes all the limitations of, a claim that is allowable in the

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present application, such claim may be subject to provisional statutory and/or nonstatutory double patenting rejections over the claims of the instant application. Once the restriction requirement is withdrawn, the provisions of 35 U.S.C. 121 are no longer applicable. See *In re Ziegler*, 443 F.2d 1211, 1215, 170 USPQ 129, 131-32 (CCPA 1971). See also MPEP § 804.01.

Claim Objections

3. Claims 1, 36, 41, 50, 55, 62, 78, and 80 are objected to because of the following informalities: non-elected subject matter is contained within the claims. Variable L, as defined in group I, is absent and cannot be any of the other groups for variable L. Appropriate correction is required.

Claims 33-35, 46-49, and 58-61 objected to because of the following informalities: they do not end with a period. Appropriate correction is required.

Claim Rejections - 35 USC § 112

4. The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

5. Claims 1-33, 35-47, 49-59, 61-70, and 74-87 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for a salt of ester of the elected group, does not reasonably provide enablement for any prodrug of formula I. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. While applicants show that an ester or salt of formula I can be produced, they have not shown that any prodrug of formula I can be produced. Jantzen and Robinson (*Modern Pharmaceuticals*, 1996, page 596) show that prodrug development requires undue experimentation in two areas: one,

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identification of an optimum substituent attached to a parent compound, and two, extensive testing in safety and efficacy of a new prodrug. In addition, a prodrug is considered a new compound and is thus a separate compound from the parent compound.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) The nature of the invention and (2) the breadth of the claims:

The claims are drawn to macrocyclic compounds that are composed of two or 3 rings.

(3) The state of the prior art and (4) the predictability or unpredictability of the art:

Compounds of the elected group are considered novel. Jantzen and Robinson show that prodrug development requires undue experimentation.

(5) The relative skill of those in the art:

One of ordinary skill in the art can replicate a procedure such as one portrayed in example 198 (page 227).

(6) The amount of direction or guidance presented and (7) the presence or absence of working examples:

The specification has provided guidance for preparation of a salt or ester of formula I.

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However, the specification does not provide guidance for preparation of a prodrug of formula I.

(8) The quantity of experimentation necessary:

Jantzen and Robinson show that prodrug development requires undue experimentation.

Considering the state of the art as discussed by the references above, particularly with regards to claims 1-33, 35-47, 49-59, 61-70, and 74-87 and the high unpredictability in the art as evidenced therein, and the lack of guidance provided in the specification, one of ordinary skill in the art would be burdened with undue experimentation to practice the invention commensurate in the scope of the claims.

6. Claims 66-70 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for the *in vitro* inhibition of NS4 or NS4A serine protease, does not reasonably provide enablement for *in vivo* inhibition of these proteases. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. Njoroge et al. (*Accounts of Chemical Research*, **2008**, 41(1), 50-59) teach that significant challenges exist in development of HCV polymerase inhibition (section titled "Challenges in discovering HCV protease inhibitors", page 52).

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in *Wands* states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (*Wands*, 8 USPQ2d 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (*Wands*, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the breadth of the claims; (3) the state of the prior art; (4) the predictability or unpredictability of the art; (5) the relative skill of those in the art; (6) the amount of direction or guidance presented; (7)

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the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Consideration of the relevant factors sufficient to establish a *prima facie* case for lack of enablement is set forth herein below:

(1) *The nature of the invention and (2) the breadth of the claims:*

The claims are drawn to a method of inhibiting HCV growth through inhibition of NS3 or NS4A protease.

(3) *The state of the prior art and (4) the predictability or unpredictability of the art:*

Njoroge et al. teach that significant challenges exist in the discovery of HCV polymerase inhibitors and their use *in vivo*.

(5) *The relative skill of those in the art:*

One of ordinary skill in the art can replicate a procedure such as one portrayed in example 215 (pages 233-34).

(6) *The amount of direction or guidance presented and (7) the presence or absence of working examples:*

The specification has provided guidance for *in vitro* inhibition of NS3 or NS4A protease using compounds of formula I.

However, the specification does not provide guidance for *in vivo* inhibition of NS3 or NS4A protease using compounds of formula I.

(8) *The quantity of experimentation necessary:*

The pharmaceutical art has been known for its unpredictability due to various conflicting pathways, or biological factors that are sometimes genetically unique to individuals. In the instant case, no data is given for evidence that compounds of formula I actually work *in vitro*. Example 215 shows a general procedure to follow. See *Hoffman v. Klaus* 9

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USPQ 2d 1657, and *Ex Parte Powers* 220 USPQ 925 regarding types of testing needed to support *in vivo* uses.

7. The following is a quotation of the second paragraph of 35 U.S.C. 112:

The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

8. Claims 70 and 74 rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. In claim 70, what polymerase, helicase, and metalloprotease are being used in combination with a compound of claim 1.

9. Claim 74 is rejected under 35 U.S.C. 112, second paragraph, as being incomplete for omitting essential steps, such omission amounting to a gap between the steps. See MPEP § 2172.01. The omitted steps are: the necessary steps to produce a compound of formula I. Currently the only definite step of the claim is attaching a heterocycle to a proline ring.

Conclusion

10. No claims are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Noble Jarrell whose telephone number is (571) 272-9077. The examiner can normally be reached on M-F 7:30 A.M - 6:00 P.M. EST.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Mr. James O. Wilson can be reached on (571) 272-0661. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

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Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see <http://pair-direct.uspto.gov>. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

/Noble Jarrell/
Examiner, Art Unit 1624

**/James O. Wilson/
Supervisory Patent Examiner
Art Unit 1624**